Acrolein

107-02-8

I. Physical and Chemical Properties

Description	Colorless or yellow liquid with piercing, disagreeable odor
Molecular formula	C_3H_4O
Molecular weight	56.1
Air concentration conversion	1 ppm = 2.3 mg/m^3 @ 25°C

II. Overview

Data both in animals *in vivo* and using human tissue *in vitro* strongly suggest that acrolein may exacerbate asthma (Roux et al., 1999; Borchers et al., 1998; Borchers et al., 1999a and 1999b; Leikauf et al., 1989a and 1989b). These studies are presented in the following sections. As described in Section II of the Introduction, OEHHA considers asthma to impact children more than adults, and thus substances that either exacerbate or induce asthma should be considered for listing under SB 25. Children have higher prevalence rates of asthma than do adults (Mannino et al., 1998). In addition, asthma episodes can be more severe due to the smaller airways of children, and result in more hospitalizations in children, particularly from the ages of 0 to 4 years, than in adults (Mannino et al., 1998; CDHS, 2000). As noted in Section II.C of this document, hospitalization is not a discretionary activity and is an indication of the severity of the asthma. Thus, on a population-wide basis, children are more impacted by asthma than adults, and since acrolein exacerbates asthma, children may be more impacted by acrolein toxicity than adults. Although it is very difficult to measure acrolein in ambient air, it appears that acrolein is an important component of air pollution, and that acrolein exposures are significant. In addition, model predictions indicate that typical urban air concentrations of acrolein exceed the chronic Reference Exposure Level (REL), which was developed to protect the public from respiratory toxicity. Thus, acrolein ranked high in the initial prioritization of TACs (see Table 1 of the Introduction). For these reasons acrolein was considered a priority chemical for evaluation of potential differential effects on infants and children.

III. Principal Sources of Exposure

Acrolein is used as a chemical intermediate in the production of acrylic acid and its esters. It is used directly as an aquatic herbicide and algicide in irrigation canals, as a microbiocide in oil wells, liquid hydrocarbon fuels, cooling-water towers and water treatment ponds, and as a slimicide in the manufacture of paper (IARC, 1985; 1995). According to the California Department of Pesticide

Regulation's (DPR's) annual pesticide use reports for 1996-1999, over 300,000 pounds of acrolein are applied in California each year, the majority of which is used on rights of way. In addition, acrolein is produced from the combustion of fossil fuels, tobacco smoke, and pyrolyzed animal and vegetable fats (IARC, 1985). As a byproduct of fires, it is one of several acute toxicants to which firefighters are exposed. Acrolein is also formed from atmospheric reactions of 1,3-butadiene. In addition to mobile source tailpipe emissions, acrolein is emitted by stationary sources. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Progam in California based on the most recent inventory were estimated to be 54,565 pounds of acrolein (CARB, 2000).

Because acrolein is extremely reactive, it is very difficult to measure in ambient air. It has been suggested that many of the measurements that have been reported in the literature underestimate actual acrolein concentrations. The California Air Resources Board (CARB) has little data on ambient concentrations of acrolein. A CARB study conducted in the early 1990s in Woodland, California, reported results of 13 outdoor measurements of acrolein (many of which were below the quantifiable limit) that ranged from 2 $\mu g/m^3$ to 8.6 $\mu g/m^3$. Indoor levels averaged 7.1 $\mu g/m^3$, and ranged up to 29 $\mu g/m^3$ (CARB, 2001). The U.S. EPA compiled data from 1961 to 1980 for two urban locations that reported a mean concentration of 14.3 $\mu g/m^3$ (6.2 ppb) with a range of concentrations from 8.2 to 24.6 $\mu g/m^3$ (3.6 to 10.7 ppb) (U.S. EPA, 1993). Acrolein has been measured in smoky indoor air. In bars and restaurants, levels between 2.3 and 275 $\mu g/m^3$ have been reported (IARC, 1995: citing Triebig and Zober, 1984; Löfroth et al., 1989). In residences where wood stoves were used, concentrations from 0.7-6.0 $\mu g/m^3$ have been reported (IARC, 1995: citing Highsmith et al., 1988). IARC (1995) noted that the acrolein concentrations in the smoke from various cigarettes ranged from 3-220 μg/cigarette. Levels as high as 463-684 μg/cigarette were reported in Japan (Kuwata et al., 1979). Jones et al. (1999) reported concentrations of acrolein in mainstream smoke (defined as smoke that is directly exhaled from the smoker) ranging from 10 – 140 μg per cigarette, and estimated concentrations in sidestream smoke (i.e., smoke emitted from the smoldering tobacco between puffs) in the range of 100 – 1700 μg per cigarette. Acrolein has also been detected in exhaust gases from both gasoline engines (0.05-27.7 mg/m^3) and diesel engines (0.12-0.21 mg/m^3) (IARC, 1995). Grosjean et al. (2001) calculated emission factors (by regression analysis of experimental data) of 0.11 mg/km from light duty vehicles and 0.72 mg/km from heavy-duty vehicles.

The U.S. EPA's Cumulative Exposure Project (CEP) provides modeling data for 148 hazardous air pollutants, including acrolein (U.S. EPA, 2000; 1990 data). The CEP data for California, primarily from urban counties, indicate that the estimated statewide annual average ambient concentration of acrolein is 0.15 $\mu g/m^3$ (95^{th} percentile = 0.3 $\mu g/m^3$). Pratt et al. (2000) examined 1990 CEP data, in addition to monitoring data when available, to assess air toxics in Minnesota. Using a hazard quotient approach, the concentrations calculated from the monitoring and modeling data were compared to cancer and noncancer health benchmark values. Pratt et al. (2000) reported that for acrolein (for which there were only modeled data), 70% of the census tracts studied exceeded the health benchmark (in this case, 0.02 $\mu g/m^3$). In addition, Pratt et al. (2000) estimated a screening level total noncancer hazard index by summing all of the noncancer hazard quotients (over all endpoints). They found that acrolein was by far the most important contributor to the noncancer hazard index. The apportionment of the hazard index for an average Minnesotan showed that acrolein accounted for 89% of the hazard index,

followed by formaldehyde at 6%, with each of the other pollutants accounting for less than 1% of the hazard index. As part of this study, Pratt et al. also did a comparison of modeling and monitoring data, where possible. While there were no monitoring data available for comparison for acrolein, Pratt et al. did find that overall there was a tendency for the modeling results to underpredict measured values.

In spite of the uncertainties regarding acrolein concentrations, it does appear that acrolein is an important irritating component of air pollution. The limited data available on ambient levels of acrolein indicate that ambient concentrations of acrolein are above the chronic REL (based on respiratory toxicity) of 0.06 $\mu g/m^3$ (0.03 ppb). Indoor air levels also have the potential to be above the chronic REL.

IV. Potential for Differential Effects

A. Summary of Key Human Studies

The argument for greater impacts of acrolein exposure in children than in adults rests on the ability of this compound to exacerbate asthma. While there are no *in vivo* human studies linking acrolein to asthma, two *in vitro* studies provide mechanistic data suggestive of a linkage.

Roux et al. (1999) investigated the interaction between passive sensitization of human isolated airways and exposure to pollutants (specifically, ozone and acrolein). Lung tissue from nonatopic, nonasthmatic patients was immunologically sensitized by incubation in sera from atopic asthmatic patients. Roux et al. reported that *in vitro* passive sensitization of the isolated tissues and exposure to acrolein act in a synergistic manner on human bronchial smooth muscle reactivity in response to both specific and nonspecific agonists. In tissues sensitized by incubation in sera from asthmatic patients, preexposure to 0.3 µM acrolein for 10 minutes or 20 minutes significantly increased the maximal contractile response to a specific antigen (*Dermatophagoides pteronyssinus*) by 20.5 ± 6.5 % and 34.9 ± 7.4%, respectively. In addition, in sensitized tissue preexposed to 0.3 µM acrolein for 10 minutes, contractile response was increased by 33.5 ± 6.2% and 32.5 ± 5.1% for carbachol and histamine, respectively.

Mucus hypersecretion is one of the hallmarks of inflammatory airway disorders, including asthma. Borchers et al. (1999b) examined the effect of acrolein on mucus glycoprotein (mucin) gene expression in airway epithelial cells. Cultured cells were treated for 4 hours with 0.01-100 nM acrolein. Borchers et al. reported that *in vitro*, acrolein can act directly on epithelial cells to increase mucin mRNA levels, or indirectly through inflammatory mediators released after acrolein exposure.

B. Summary of Key Animal Studies

In vivo animal studies provide support for the contention that acrolein exposure may exacerbate asthma. First, acrolein induces bronchial hyperresponsiveness, a key characteristic of asthma, in guinea pigs. Leikauf et al. (1989a) investigated the onset and time course of increases in pulmonary resistance and bronchial responsiveness to intravenous acetylcholine in guinea pigs exposed to acrolein. First, animals were exposed to <0.01 (sham), 0.31, 0.67, 0.94, or 1.26 ppm acrolein for 2 hours. Pulmonary resistance was immediately increased (first measured 5 minutes after cessation of acrolein exposure) and

returned to base-line within 25 minutes (0.31 ppm) and 60 minutes (1.26 ppm) post exposure. Second, bronchohyperresponsiveness was assessed by measuring the change in specific total pulmonary resistance induced by acetycholine either before (control) or 1, 2, 6, or 24 hours after a 2-hour exposure to 0.94 ppm acrolein. In contrast to the transient increase in base-line pulmonary resistance observed in the first experiment, acrolein exposures of greater than 0.94 ppm produced a persistant change in bronchoresponsiveness to intravenous acetylcholine. Increased bronchoresponsiveness was evident at 1 hour and became maximal 2-4 hours after exposure. The concentration of acetylcholine necessary to double pulmonary resistance (ED200) decreased from 104.2 ± 7.3 (µg/kg/min) prior to acrolein exposure to 79.6 ± 15.9 at 1 hour after cessation of acrolein exposure. At two hours, ED200 was 32.5 ± 7.9. This effect persisted with significant increases in bronchoresponsiveness at 6 and 24 hours following acrolein exposure.

Leikauf et al. (1989b) confirmed the results of the previous study, and also observed an association between acrolein-induced bronchial hyperresponsiveness and increased sulfidopeptide leukotriene (LT) C_4 concentration in lung lavage fluid of guinea pigs. Sulfidopeptide leukotrienes are bronchoconstrictive lipid mediators thought to have an important role in the pathophysiology of asthma. In this study, guinea pigs were exposed to 1.3 ppm acrolein for 2 hours. Following acrolein exposure, bronchial responsiveness to intravenous acetylcholine was determined after administration of a leukotriene receptor antagonist (L-649,923) or leukotriene formation inhibitors (L-651,392 and U-60,257). Both the leukotriene receptor antagonist and the leukotriene formation inhibitors attenuated acrolein-induced hyperresponsiveness and bronchoconstriction. In addition, the leukotriene inhibitor L-651,392 reduced the increase of immunoreactive LTC_4 concentrations in lavage fluid following acrolein exposure.

As previously noted, mucous hypersecretion is one of the hallmarks of respiratory diseases, including asthma. Borchers et al. (1998) studied mucin gene expression and mucus hypersecration in respiratory tissues of rats exposed to acrolein. Animals were exposed to 3 ppm acrolein, 6 hours per day, 5 days per week, for 2 weeks. Results of this study demonstrate that acrolein exposure induces mucous cell hyperplasia and metaplasia in airway surface epithelium and airway lumen, accompanied by increased mucin mRNA and mucin glycoproteins. The percentage of mucous cells increased to approximately the same level in small (≤0.8-mm-diameter) and large (>0.8-mm-diameter) airways, yet the magnitude of the effect was greater in the small airways where mucous cells are normally rare or absent. In small airways, cells increased 270-fold in exposed animals (from 0.02% of cells in control animals) while in large airways, mucus cells increased 26-fold (from 0.23% of cells in controls). In the trachea (large airway), mucin mRNA increased within 2 days of exposure and was accompanied by an increase in mucin glycoproteins on the surface of the airways and submucosal gland epithelium compared to controls. In the lung (small airway), increases in mucin mRNA and mucin glycoproteins were observed on days 5 and 9 of exposure. Increased mucin glycoproteins were detected within the lumen and airway epithelium of the lung on day 12.

Borchers et al. (1999a) examined the effects of acrolein exposure on mucin gene expression in mice. In this study, animals were exposed to 3.0 ppm acrolein, 6 hours/day, 5 days/week for 3 weeks. Acrolein increased mucin mRNA levels in the lung in a time-dependent manner, becoming significantly greater than controls at day 12 (5-fold increase), and increasing further after 3 weeks of exposure (10-fold

increase). Mucin glycoproteins were found in cytoplasmic granules of mucous cells, on apical surface epithelium and in the airway lumen of exposed mice, but were not found in unexposed mice or mice exposed up to one week. The acrolein-induced increase in mucin mRNA and mucin glycoproteins was associated with a significant increase in macrophages (indicative of an inflammatory response) recovered in bronchoalveolar lavage (BAL) fluid. The magnitude of macrophage cell increase was correlated with the increase in mucin mRNA levels. While the macrophage effect developed over 2-3 weeks exposure, acrolein caused an immediate increase in neutrophils in BAL fluid, observed on day 1 of exposure; however by day 5 and for the remainder of the experiment neutrophil numbers were similar in control and exposed animals.

V. Additional Information

A. Other Respiratory Toxicity

Although not all respiratory irritants are associated with the exacerbation of asthma, it is interesting to note that acrolein is a potent irritant of the respiratory tract and eyes in both animals and humans. In animal studies, chronic exposure of rats to acrolein (0.4 to 5 ppm) resulted in bronchopneumonia, obstructive lesions in small and large airways, histological changes to the nasal turbinates (increased submucosal lymphoid aggregates) as well as the pulmonary epithelium and mucosa, rhinitis, lung lesions, epithelial necrosis of the peribronchiolar and bronchiolar regions, alveolitis, hemmorhage, hyperplasia and metaplasia of the airway epithelium, and inflammatory alterations (Kutzman, 1981; Kutzman et al., 1985; Feron et al., 1978; Lyon et al., 1970; Leach et al., 1987). In mice, acrolein exposure (1.7 ppm; 6 hours/day; 5 days) produced severe exfoliation and squamous metaplasia of the respiratory epithelium, and ulceration of the olfactory epithelium (Buckley et al., 1984). Similar respiratory effects have also been reported in monkeys, dogs, hamsters and rabbits (Feron et al., 1978; Lyon et al., 1970). The RD_{50} (concentration required for depression of the respiratory rate of mice by 50%) was estimated as 1.7 ppm (Kane et al., 1979).

B. Regulatory Background

Acrolein is a federal hazardous air pollutant and was identified as a toxic air contaminant in California in April 1993 under AB 2728. OEHHA has adopted an acute non-cancer reference exposure level (REL) of 0.19 $\mu g/m^3$ (0.09 ppb) and a chronic REL of 0.06 $\mu g/m^3$ (0.03 ppb) for acrolein (OEHHA, 1999; OEHHA, 2001). Acrolein is not listed under Proposition 65.

In 1985, The International Agency for Research on Cancer (IARC) reviewed the available data on acrolein and found inadequate evidence in both humans and experimental animals to evaluate the potential carcinogenicity of acrolein to humans (IARC, 1985; IARC, 1995). However, a metabolite of acrolein, the reactive epoxide glycidaldehyde, has been shown to be mutagenic and carcinogenic in mice and rats. Therefore, acrolein has been designated by U.S. EPA as a Group C substance, with possible human carcinogenic potential (U.S. EPA, 1994).

VI. Conclusions

In vivo data in animals and *in vitro* data using human tissue strongly suggest that acrolein may exacerbate asthma (Roux et al., 1999; Borchers et al., 1998; Borchers et al., 1999a and 1999b; Leikauf et al., 1989a and 1989b). Asthma is a disease that disproportionately impacts children (see Introduction Section III.). Therefore, OEHHA has placed acrolein into Tier 1.

VII. References

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